ORIGINAL

TSCA NON-CONFIDENTIAL BUSINESS INFORMATION

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DOES NOT CONTAIN CBI

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April 11, 2013

Office of Pollution Prevention and Toxics
Document Processing Center (Mail Code 7407M)
U.S. Environmental Protection Agency
1201 Constitution Ave., NW
EPA East Room 6428
Washington, DC 20004
Attention: 8(e) Coordinator

RE: Notification of Substantial Risk

Dear Sir or Madam:

In accordance with Section 8(e) of the Toxic Substances Control Act (TSCA), Solvay Chemicals, Inc. is submitting the following information:

As part of the testing program to support REACH registration in Europe, a material, identified for REACH registration as "Diisopentyl ether", CAS# 544-01-4, was tested in a series of studies. As part of that series, the following studies were conducted:

- "Determination of the Genotoxic Potential of Diisopentyl ether with the *In vitro* Mammalian Micronucleus Test in Human Lymphocytes"
- "Determination of the Mutagenic Potential of Diisopentyl ether with the Bacterial Reverse Mutation Test"
- "Micronucleus Test in Bone Marrow Cells of the Mouse with Diisopentyl ether"

In the *in vitro* Mammalian Micronucleus Test, diisopentyl ether was tested in the absence of a metabolic activation system (S9 mix) at concentrations from 20 to 40 µg/L, and in the presence of S9 at concentrations from 150 to 400 µg/L. A relevant increase in the number of cells containing micronuclei was observed at higher concentrations, both with and without the S9 mix. The laboratory reported that, under experimental conditions, diisopentyl ether does induce the formation of micronuclei in human lymphocytes *in vitro*.

Diisopentyl ether was also tested in the *Salmonella typhimurium* reverse mutation assay. The test was performed in three independent experiments, in the presence and absence of the S9 mix. In the first experiment, Diisopentyl ether, at concentrations from 50 to 5012 µg/plate, did not cause a significant increase in the number of revertant colonies in the tested strains. The laboratory concluded that the test material did not show any mutagenic effects.
In a second study, at concentrations from 313-5008 µg/plate, the test substance showed mutagenic effects in 2 of the 5 strains tested (TA98 and TA1535). This effect was also found in the third study, where the test substance showed mutagenic effects in the same strains (TA98 and TA1535). The laboratory reported that diisopentyl ether was mutagenic under these test conditions.

In the *in vitro* mouse micronucleus test, male animals were dosed with diisopentyl ether via oral gavage at levels of 500, 1000, or 2000 mg per kg body weight, with 5 animals per level. No treatment-related clinical signs or mortality were noted in any animal. Bone marrow of the 2000 mg/kg dose group was sampled 24 or 48 hours after dosing, with bone marrow of the negative and positive control groups harvested concurrently.

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No increase in the mean frequency of micronucleated polychromatic erythrocytes was observed in the bone marrow of animals treated with diisopentyl ether. The groups that were treated with the test substance showed no decrease in the ratio of polychromatic to normochromatic erythrocytes compared to the concurrent vehicle control group, indicating a lack of toxic effects of this test substance on erythropoiesis. The laboratory reported that, under these *in-vivo* test conditions, the test substance was neither clastogenic nor aneugenic in the bone marrow micronucleus, up to the maximum dose tested.

Solvay Chemicals Inc. does not believe that this substance presents an unreasonable hazard to workers or to the public when properly used in its intended applications. However, we believe that this information may meet EPA's reporting criteria for TSCA Section 8(e), and we therefore are submitting these data as a matter of good Product Stewardship.

This information was communicated to Solvay Chemicals on March 14, 2013.

Additional data that were communicated to Solvay Chemicals at the same time as these studies were:

- Local Lymph Node Assay (LLNA) In Mice with Diisopentyl ether
- Assessment of Acute Inhalation Toxicity with Diisopentyl ether in the Rat (Acute Toxic Class Method)
- Combined 28-Day Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test of Diisopentyl ether in Rats By Oral Gavage

In the local lymph node assay, animals were exposed to the test substance in concentrations of 25, 50% (w/v) and 100%. The animals did not show any signs of systemic toxicity or local skin irritation during the course of the study and no cases of mortality were observed. In this study Stimulation Indices (S.I.) of 1.74, 5.39 and 9.68 were determined in the test item at concentrations of 25 and 50% in a blend of acetone and olive oil and 100% (undiluted test item), respectively. The laboratory reported that a clear dose response was observed, and the test substance was a skin sensitizer under the test conditions.

In the acute inhalation study, Diisopentyl ether was administered as a vapor by inhalation for 4 hours to two groups of three male and three female Wistar rats. Animals were observed daily and body weight measurements were taken on Days 1, 2, 4, 8 and 15. Macroscopic examination was performed on the day of death or after terminal sacrifice (day 15). At a dose level of 2 mg/L, no clinical signs were noted during and after exposure. At 7 mg/L, slow breathing was noted in two males and one female during exposure. After exposure, hunched posture, labored respiration and piloerection were seen in all animals on Day 1. The 4-hour LC50 value was determined by the laboratory to be between 2 – 10 mg/L.

In the 28-day repeated dose study, four groups of ten male and ten female Wistar Han rats were exposed by oral gavage to the test substance at 0, 100, 300 and 1000 mg/kg/day. Males were exposed for 29 days, i.e. 2 weeks prior to mating, during mating, and up to termination. Females were exposed for 41-47days, i.e. during 2 weeks prior to mating, during mating, during postcoitum, and during at least 4 days of lactation. The parental, reproduction and developmental No Observed Adverse Effect Levels (NOAELs) were determined to be ≥ 1000 mg/kg/day (the highest dose level). Treatment-related microscopic findings were noted in the 1000 mg/kg treated rats in the thyroid (males), thymus (females) and liver (both sexes), and in the kidneys (males) of the 100, 300 and 1000 mg/kg treated rats. Hyperplasia/hypertrophy of the follicular epithelium of the thyroid was recorded for males in 1 rat at the 0 mg/kg, in 1 rat at the 100 mg/kg and in 5 rats at the 300 mg/kg levels and in 3 rats at the 1000 mg/kg level. The laboratory reported that this finding may reflect an increase in thyroxine production in response to feedback mechanisms as a result of increased turnover of thyroxine by the hypertrophic hepatocytes, the thus the laboratory concluded the increase in severity in the 1000 mg/kg treated male rats was considered to be a non-adverse effect.

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Also in this study lymphoid atrophy of the thymus was noted in 1 rat at the 100 mg/kg level and 3 female rats at the 1000 mg/kg level. At 1000 mg/kg, decreased thymus weights were noted for the females and males. As microscopic examination showed only a minimal increase in incidence and/or severity, the lab concluded that this finding was also not adverse. Hepatocellular centrilobular hypertrophy was noted in all 1000 mg/kg treated. Concurrently, increased liver weights were noted for mid and high dose females and high dose males, and liver enzyme levels (ALAT, ASAT, ALP) were increased for several treated animals. In absence of any other histopathologic indicators of liver toxicity these findings were considered to be non-adverse. Males at all dose groups showed a dose related increase in incidence and severity of hyaline droplets in the kidneys. Hyaline droplets were considered to represent alpha2u-globulin, a normal protein in male rats which undergoes re-absorption in the proximal cortical tubules. In addition, increased kidneys weights were noted for males and females at 1000 mg/kg. For the males, this might be related to the occurrence of hyaline droplets. For females, no corroborative findings were noted. Without any other treatment-related microscopic changes in the kidney or other corroborative findings, the presence of hyaline droplets and the slightly increased kidneys weight were considered to be nonadverse.

In this study, a motor activity test conducted at the end of treatment revealed decreased counts for females of all dose groups, however without a clear dose related trend and only statistically significant for total counts at the mid dose. As other functional and clinical observations did not show any abnormalities, this finding was considered not to be adverse.

Solvay Chemicals asserts that none of the information contained within this notice constitutes confidential business information (CBI) under TSCA.

Should you have any questions, or require further information, please do not hesitate to contact Dr. Marc. Feldman at (713) 525-6575. Thank you.

Sincerely,

David M. Henry
Vice President, Peroxygens
Solvay Chemicals, Inc.

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